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## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 16 August 2000 (16.08.00)	
<b>International application No.</b> PCT/DK99/00720	<b>Applicant's or agent's file reference</b> P 99 061 WO
<b>International filing date</b> (day/month/year) 20 December 1999 (20.12.99)	<b>Priority date</b> (day/month/year) 21 December 1998 (21.12.98)
<b>Applicant</b> SØRENSEN, Jens, Christian, Hedemann et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

14 July 2000 (14.07.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b>  F. Baechler  Telephone No.: (41-22) 338.83.38
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REC'D 26 MAR 2001

WIPO

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference P 99 061 WO		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/DK99/00720	International filing date (day/month/year) 20/12/1999	Priority date (day/month/year) 21/12/1998	
International Patent Classification (IPC) or national classification and IPC G01N1/00			
Applicant HISTOTECH APS et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 9 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  14/07/2000	Date of completion of this report  22.03.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Loades, M  Telephone No. +49 89 2399 2184 

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK99/00720

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

### Description, pages:

1-12 as originally filed

### Claims, No.:

1-39 as received on 21/02/2001 with letter of 21/02/2001

### Drawings, sheets:

1/11-11/11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/DK99/00720

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 39.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 39.

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)

Yes: Claims 1-26,28-38

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK99/00720

	No:	Claims	27
Inventive step (IS)	Yes:	Claims	30,32-36
	No:	Claims	1-29,31,37,38
Industrial applicability (IA)	Yes:	Claims	1-38
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/DK99/00720

**R Item I**

**Basis of the report**

The original support for a broad statement as set out in claim 39, as far as it can be understood, cannot be found, so that this appears to extend the subject matter beyond the original disclosure.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The following documents were cited in the search report:

- D1: DATABASE WPI Section Ch, Week 199542 Derwent Publications Ltd., London, GB; Class J04, AN 1995-323601 XP002900963 & JP 07 218398 A (SEITAI KAGAKU KENKYUSHO KK), 18 August 1995 (1995-08-18)
- D2: DE 43 23 483 A (KATHREIN ANTON DR) 24 February 1994 (1994-02-24)
- D3: DATABASE WPI Section EI, Week 199939 Derwent Publications Ltd., London, GB; Class S03, AN 1999-463078 XP002900964 & JP 11 194076 A (MURAZUMI KOGYO KK), 21 July 1999 (1999-07-21)
- D4: US-A-5 282 404 (LEIGHTON STEPHEN B ET AL) 1 February 1994 (1994-02-01)
- (D5: DE 197 43 590 A (ENGEL BRIGITTE) 6 May 1999 (1999-05-06) P-document, published after priority date of present application)
- D6: EP-A-0 245 969 (CAMBRIDGE INSTRUMENT CO) 19 November 1987 (1987-11-19)

2. Novelty and inventive step:

**Introductory remark (possible lack of unity):**

It is noted that no inventive step has been found in the subject matter of claims 1-26, so that the only possible (single) invention seems to occur in claims 32, etc., thus lack of unity has not been raised formally. If somehow the presence of an inventive step were proved in the series of claims 1-26, then an objection of lack of unity would probably have arisen, since there would appear to be no common subject matter between the two sets of claims, which provide special technical features in common. Detailed

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/DK99/00720

comments are not given here, and thus this does not represent an exhaustive argumentation in respect of lack of unity, which would have to be made in relation to the prior art document(s).

**Claims 1-26**

Claim 1: This merely relates to positioning a tissue block and cutting it simultaneously into a multiple of sections. This basic idea known from D1, in which the cutter has five blades 1. Claim 1 also refers to the slices having an orientation corresponding to an orientation of a plane of a preceding scanning, but this "preceding scanning" is not a definite step of the method, so that the nature of the correspondence is not clear (see Item VIII below). Even if this claim were amended to clearly restrict it to a scanning step, or if were considered that it is already so restricted, this would appear to be an obvious measure. If such a sample is to be scanned by e.g. CT, MRI etc. this would be done on the whole sample, and it would be logical then to ensure that there were some correspondence between the orientation of the sample during slicing and the scanning set-up, so that useful information could be subsequently derived.

Claim 8: D1 discloses an apparatus for cutting a tissue block in slices in a predetermined orientation, which would be **suitable for** correlation with scanning information. The sectioning means comprises five blades 1. A support surface would obviously be necessary, and driving means of some description must be employed to move the blades through the sample.

Thus the subject matter of claim 8 is not inventive.

Dependent claims 2-7,9-26: These dependent claims seem to relate to mere design modifications, consequential features of the basic system of claims 1 and 8, or conventional features, and thus do not add anything inventive to these claims:

claim 2: known from D1

claim 3: claim not clear, but, as far as can be understood, matter of choice on part of operator.

claims 4, 15, 19, 22: suction techniques for holding specimens are apparently well known, though no document has been cited in the search report.

claim 5: obvious design features.

claim 6, 20,21: obvious technique to avoid sticking of blades.

claim 7: obvious procedure.

claim 9: known from D1.

claim 10: it is not clear how this aim is achieved: page 8, line 10 refers to spacing blocks of different thickness. This appears to be an obvious option.

claims 11- 13: obvious possibilities.

claim 14, 16-18: for accurate medical work, accurate positioning means would be an obvious necessity.

claim 23-26: apparently conventional driving means.

**Claims 27-38:**

Claim 27: All this appears to claim is basically embedding a tissue sample or organ in a polymer moulding material, by holding the tissue sample or organ relative to one surface of the mould while the polymer is soft.

This seems to be exactly what is done in D6 (see abstract , e.g. lines 10-20). The base of the mould cassette can be said to act as the reference surface, or the walls 16 (see e.g. col. 8, lines 19-32). There is no reason to consider that the method would be unsuitable for use in the method of claim 1.

Claims 28, 29, 31 do not appear to add anything inventive to claim 27.

**Claim 32:**

In D6, the sample is inserted in a cassette, clamped, then the cassette is inverted, and then immersed in plastics embedding material. There appear to be no pivot members for pivoting a reference mould when embedding the sample.

Thus claims 32-36, and claim 30, which refers to pivoting, as far as they can be understood, appear to be novel and inventive.

**Claims 37-38:**

Claim 37 seems to be obvious, since D4 refers to the use of plastics as an embedding material (see e.g. col. 1, line 19), and non-toxic is an obvious requirement of such a material in this particular application. Claim 38 relates to conventional moulding procedures.



**Re Item VII**

**Certain defects in the international application**

- 1 Reference numerals should have been inserted in the claims (in particular the apparatus claims), to aid identification of the features of the claims in the figures.
2. Documents D1 to D4, and D6 should have been referred to in the description.

**Re Item VIII**

**Certain observations on the international application**

Claims 1,8:

Claim 1 refers to the slices having an orientation corresponding to an orientation of a plane of a preceding scanning, but this "preceding scanning" is not a definite step of the method, so that the nature of the correspondence is not clear. It would appear that a definite step of scanning the tissue block, with details of how it is positioned etc., should have been introduced into the claim. Claim 8 seems to be only limited to a cutting apparatus, again with no particular restriction with regard to scanning; this might have been solved by having a system claim with the scanning apparatus and the cutter, as parts thereof.

It is noted that in interpreting the scope of this claim the passage commencing "such as..." have been ignored.

Claim 27: The scope is not clear. It is not clear if the term "embedding" is standard in the art. The expression "in order to obtain a tissue block that is provided with reference positions" is not clear.

The restrictive effect of the passage "(for) use in a method according to claim 1 to 7 and an apparatus according to any of claims 8 to 26", is not clear.

Claim 32: The restrictive effect of the phrase "according to .....claims 8 to 26", is not clear.

The construction of the apparatus does not clearly emerge, and it is difficult to identify the various parts in the description and drawings. A "tubular side portion" cannot be found, nor a "retractable tubular side wall".

Claim 37: The scope is very obscure, particularly since the term "tissue embedding" seems unusual, and because of the various references to previous claims and the preferred or exemplary features, so that its subject matter seems to resolve simply to a non-toxic embedding plastic around a tissue sample or organ. It is not clear how to relate the phrase "whereby a tissue block..." to the rest of the claim. The reference to "alginate" seems to be a preferred feature rather than a limitation.

## REVISED PATENT CLAIMS:

1. A method of cutting of a tissue block of an internal organ or other internal anatomical structures into slices having a predetermined orientation in the tissue block corresponding to an orientation of a plane of a preceding scanning, such as a CT, MR or PET scanning, wherein the tissue block is placed in a predetermined position with respect to a multiple of cutting members and then simultaneously sliced into a multiple of sections.
2. A method according to claim 1, whereby the simultaneous sectioning is performed by a multiple of cutting members oriented in parallel.
3. A method according to claim 1 or 2, whereby the tissue block is positioned relative to the cutting members in a predetermined orientation corresponding to the orientation of tissue block in vivo.
4. A method according to any of the previous claims, whereby the tissue block is placed for cutting on a support surface and held in the predetermined position by applying a vacuum to one or more suction pads in the surface underneath the tissue block.
5. A method according to claim 1 to 4, wherein the cutting members are mounted on a frame for engaging and sectioning the tissue block placed underneath the cutting members.
6. A method according to claim 5, whereby the cutting members are vibrated during the cutting action.
7. A method according to any of the previous claims, whereby the tissue block is centrally positioned on the support surface before the cutting action.

8. An apparatus for cutting of a tissue block in slices with a predetermined orientation in the tissue block for obtaining a direct correlation of CT, MR or PET images for pathological examination, said apparatus comprising
- 5 a support surface for receiving a tissue block,
- sectioning means comprising a multiple of cutting members, and
- driving means for moving the sectioning means towards the support surface for
- 10 slicing a tissue block into sections.
9. An apparatus according to claim 8, wherein the sectioning means comprise a multiple of parallel cutting members arranged in a cutting frame.
- 15 10. An apparatus according to claim 8 or 9, wherein the distance between the cutting members can be adjusted.
11. An apparatus according to any of the claims 8 to 10, wherein the tension of the cutting members can be adjusted.
- 20 12. An apparatus according to any of the claims 8 to 11, wherein the cutting members are razor blades.
13. An apparatus according to any of the claims 8 to 11, wherein the cutting
- 25 members are wires.
14. An apparatus according to any of the previous claims, wherein the support surface is provided with positioning means for allowing accurate positioning of a tissue block, preferably embedded in an embedding having predetermined reference
- 30 surfaces.

15. An apparatus according to any of the previous claims, wherein the support surface is provided with vacuum supply means for retaining the tissue block in a predetermined position.
- 5 16. An apparatus according to claim 14 or 15, wherein a centring means with a laser pointer are provided for accurate positioning of the tissue block on the support surface.
- 10 17. An apparatus according to the claims 14 to 16, wherein concentric centring marking circles are provided in the support surface and possibly supplemented with aiming crossing lines.
18. An apparatus according to the claims 14 to 16, wherein concentric recesses are provided in the support surface.
- 15 19. An apparatus according to any of the claims 14 to 18, wherein concentric circular suction rings are provided that can be supplied with vacuum from the vacuum supply means for retaining the tissue block.
- 20 20. An apparatus according to any of the previous claims, wherein the cutting members are connected to vibration means for vibration during the slicing action.
21. An apparatus according to claim 20, wherein the vibration means comprise a pneumatic vibrator that is connected to pneumatic supply means.
- 25 22. An apparatus according to claim 21 and any of the claims 14 to 19, wherein the vacuum in the vacuum supply means is generated by vacuum generating means connected to the pneumatic supply means.
- 30 23. An apparatus according to any of the claims 8 to 22, wherein the driving means comprise pillar guiding means provided on the support surface and linear actuation

means for linear movement of the sectioning means towards the support surface along the path defined by the pillar guiding means.

24. An apparatus according to claim 23, wherein the linear actuation means comprise  
5 a threaded driving spindle parallel to the pillar guide means and a corresponding threading in the cutting frame.

25. An apparatus according to claim 24, wherein the threaded driving spindle is provided with a handle for manual operation.

10

26. An apparatus according to claim 23, wherein the driving spindle is pneumatically, hydraulically or electrically driven.

27. A method of preparing a tissue block for pathological examinations by encasing  
15 the tissue block in a tissue embedding in order to obtain a tissue block that is provided with reference positions for use in a method of cutting the tissue block according to any of claims 1 to 7 in an apparatus according to any of claims 8 to 26, said method comprising the steps of

20 filling a moulding form with an appropriate amount of non-toxic, biologically inert polymer moulding material, said form having at least one reference surface, and positioning a tissue block in said polymer moulding material in a predetermined position relative to said at least one reference surface, while the polymer moulding material is in its soft state.

25

28. A method according to claim 27, whereby the tissue block is positioned in the polymer material with an orientation that corresponds to the orientation of the tissue block in vivo.

30 29. A method according to claim 27 or 28, whereby the tissue block is embedded in a bottom mould part and a top mould is formed in a top moulding form that is filled with polymer moulding material and placed on top of the lower moulding part with a

partly encased tissue block, so that the tissue block is completely encased by the moulding.

30. A method according to any of the claims 27 to 29, whereby the tissue block is  
5 fixed to a reference moulding of predetermined dimensions and whereby said reference moulding is pivoted into a predetermined position in one or more directions, and then moulded into at least a bottom moulding.

31. A method according to any of the claims 27 to 30, whereby the polymer material  
10 is a cold polymerisate that polymerises by addition of water, such as a alginate plastic polymer.

32. An apparatus for producing a tissue embedding according to a method according  
15 to any of the claims 27 to 30 for use in an apparatus according to any of the claims 8 to 26, said apparatus comprising

first moulding means defining a reference moulding form for embedding a tissue  
block in a moulding, said first moulding means comprising an tubular side portion  
and first bottom plate means providing a bottom surface in the reference moulding  
20 form,

positioning means comprising at least one set of pivoting means for pivoting a  
reference mould, and

25 second moulding means for defining a bottom moulding form, said second moulding means comprising a retractable, tubular side wall and a second plate means for providing a bottom surface in the bottom moulding form.

33. An apparatus according to claim 32, wherein third moulding means are provided  
30 for defining a top moulding form, said third moulding means comprising a tubular side wall form with a cross section generally corresponding to the tubular side wall of the second moulding means.

34. An apparatus according to claim 32 or 33, wherein a centrally disposed, retractable piston having a hemispherical end portion that extends into and forms part of the reference mould form when extended.

5

35. An apparatus according to any of the claims 32 to 34, wherein the pivoting means comprise two oppositely disposed, aligned pins that are provided in the outer edge region of the second moulding means and are radially insertable in the reference mould defining a pivot axis for pivoting the reference mould into a desired position.

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36. An apparatus according to claim 35, wherein two sets of pivoting means are provided defining two preferably mutually orthogonal pivot axes.

37. A tissue embedding for providing predetermined reference surfaces for accurate positioning of a tissue block in an apparatus according to any of the claims 8 to 26 for the performance of a method according to any of the claims 1 to 7, whereby a tissue block, such as an internal organ, or another internal anatomical structure is at least partly fixed in a mould having a predetermined reference surface, preferably a bottom surface for accurate positioning in an apparatus for sectioning said tissue block for pathological examination purposes, said tissue embedding comprising mould parts made of a non-toxic plastic polymer material, in particular an alginate plastic polymer.

38. A tissue embedding according to claim 37, wherein the tissue block is provided with a bottom mould part and a top mould part encasing the tissue block inside said mould parts.

39. A method of placing a reference grid on a section of a tissue block from an apparatus according to claim 8, whereby said reference grid allows a direct correlation of one or more tissue volumes to corresponding digital imaging volumes from CT, MR or PET imaging modalities.